Reporting to clinicians: the breakpoint issue

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Disclosures

- Speaker's honoraria from Cubist, Cepheid, Wyeth, AstraZeneca and Meda
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- Research collaboration (one project) with bioMérieux
- Advisory board 1928 diagnostics
- Member of the steering committee (and chairman-elect) of EUCAST

Key topics

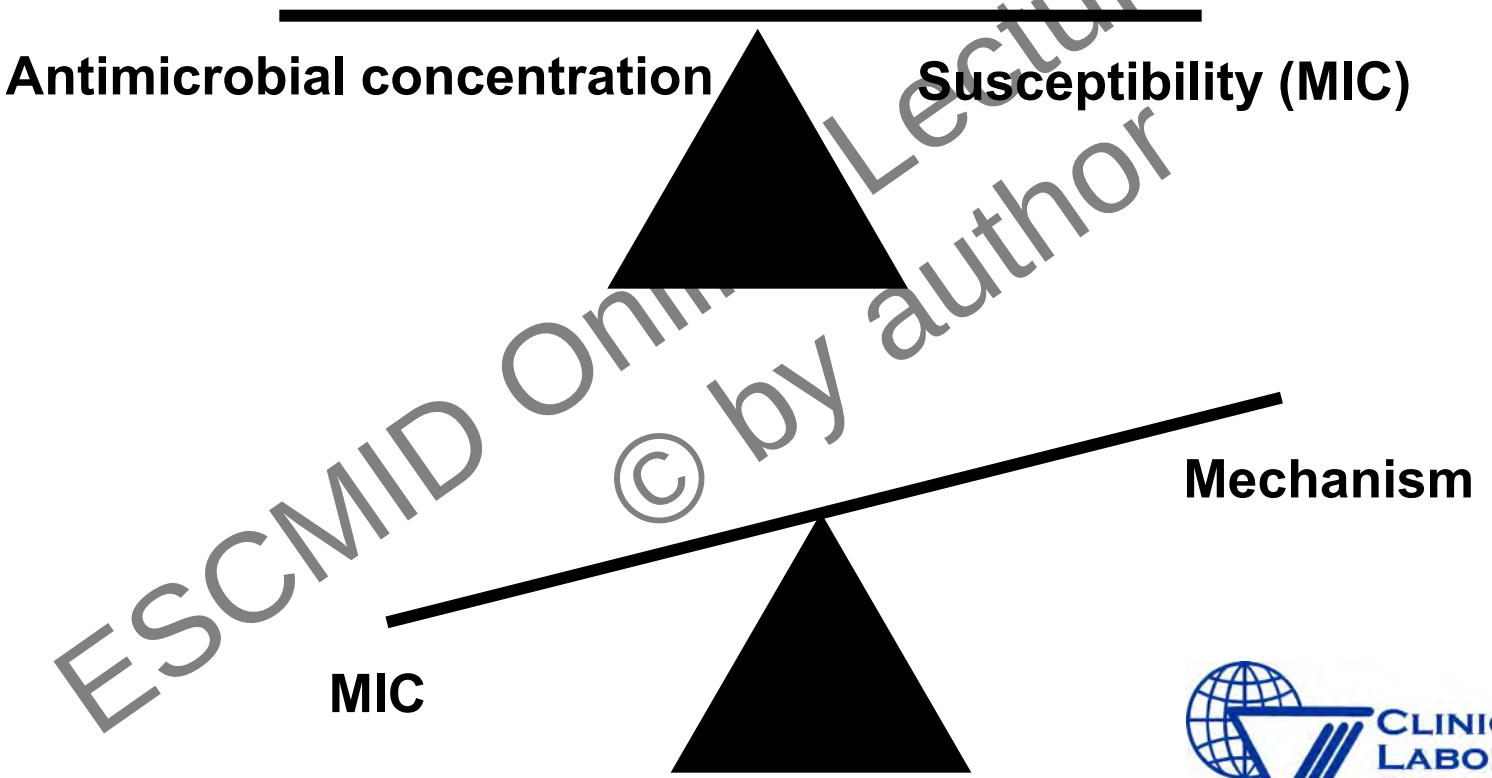
- Some initial words on therapeutic outcome and MIC determination
- MIC vs mechanism: carbapenems

General remarks on outcomes and MICs – basics for the discussion

Some words on therapeutic outcome

- Not all patients with susceptible strains respond
- Not all patients with resistant strains fail treatment
- Co-morbidities and co-infections need to be taken into consideration
- Some patient populations are particularly difficult to judge regarding therapeutic outcome

The MIC paradigm



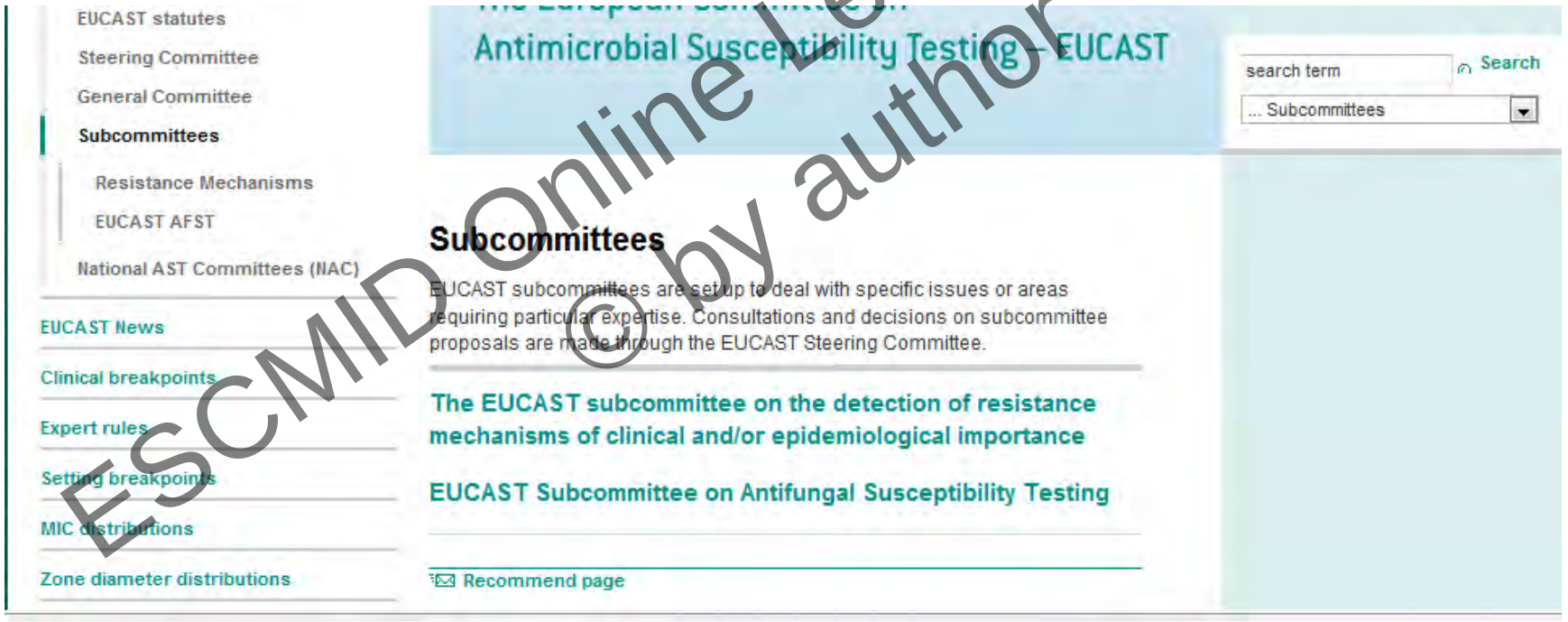
Karolinska Institutet

CLINICAL AND LABORATORY STANDARDS INSTITUTE ™

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

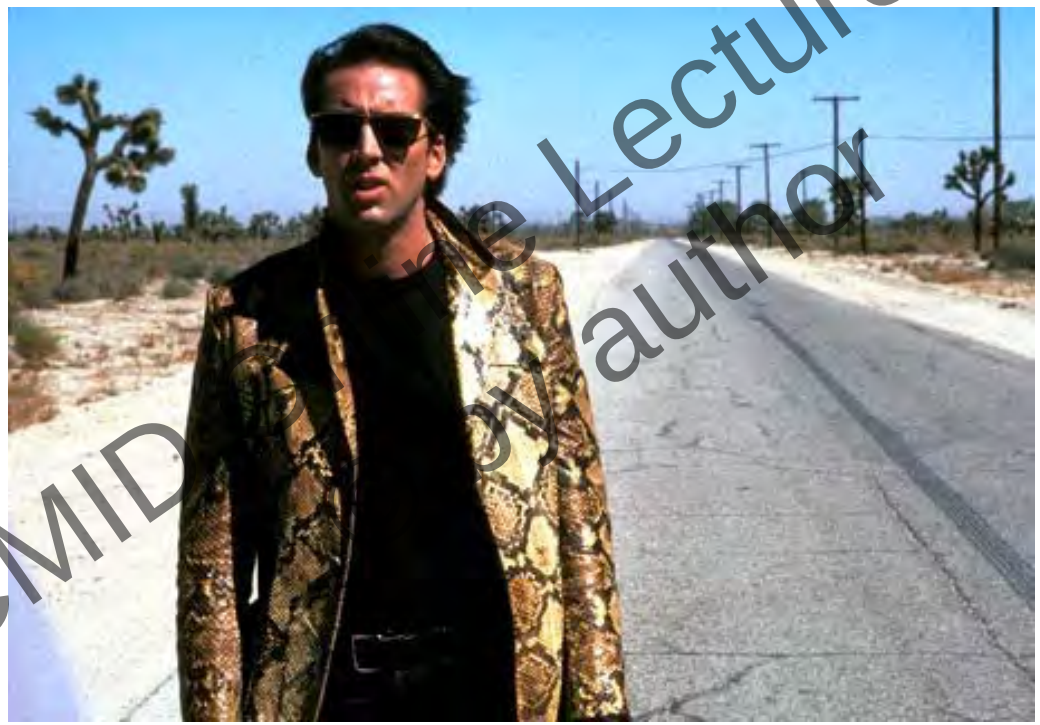
Breakpoint committees do not have a general lack of interest in mechanisms…



Some major issues with MIC-testing

- You (almost) always get a result
- Since you get a result you assume it must be correct
- Automated AST machines purchased to do MIC-testing have to be correct, since they were so expensive….

Find other ways of expressing yourself than MIC-testing….



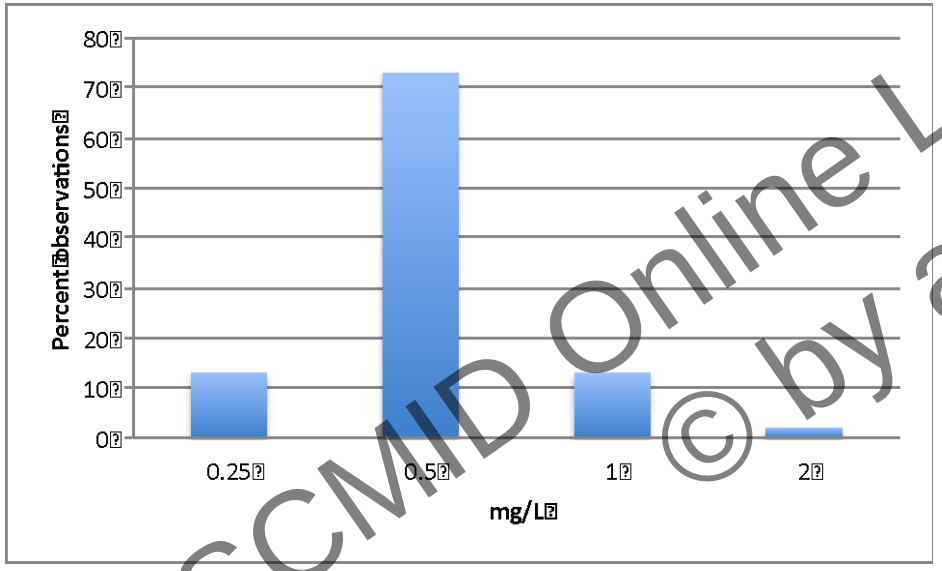
Did I ever tell you that this here jacket represents a symbol of my individuality and my belief in personal freedom?

Nick Cage, Wild at Heart (David Lynch 1990)

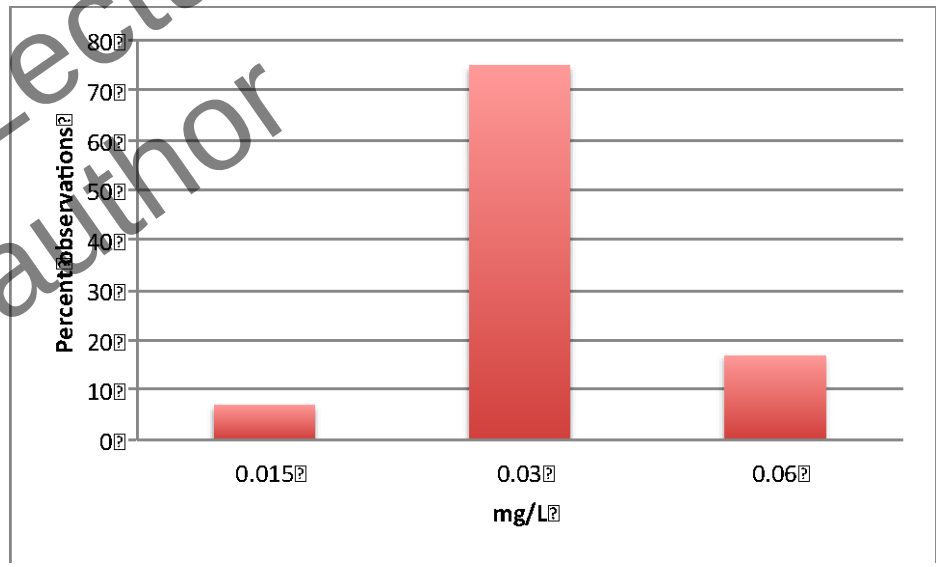
You need to follow the recipe…….

Reproducibility of broth microdilution

K. pneumoniae



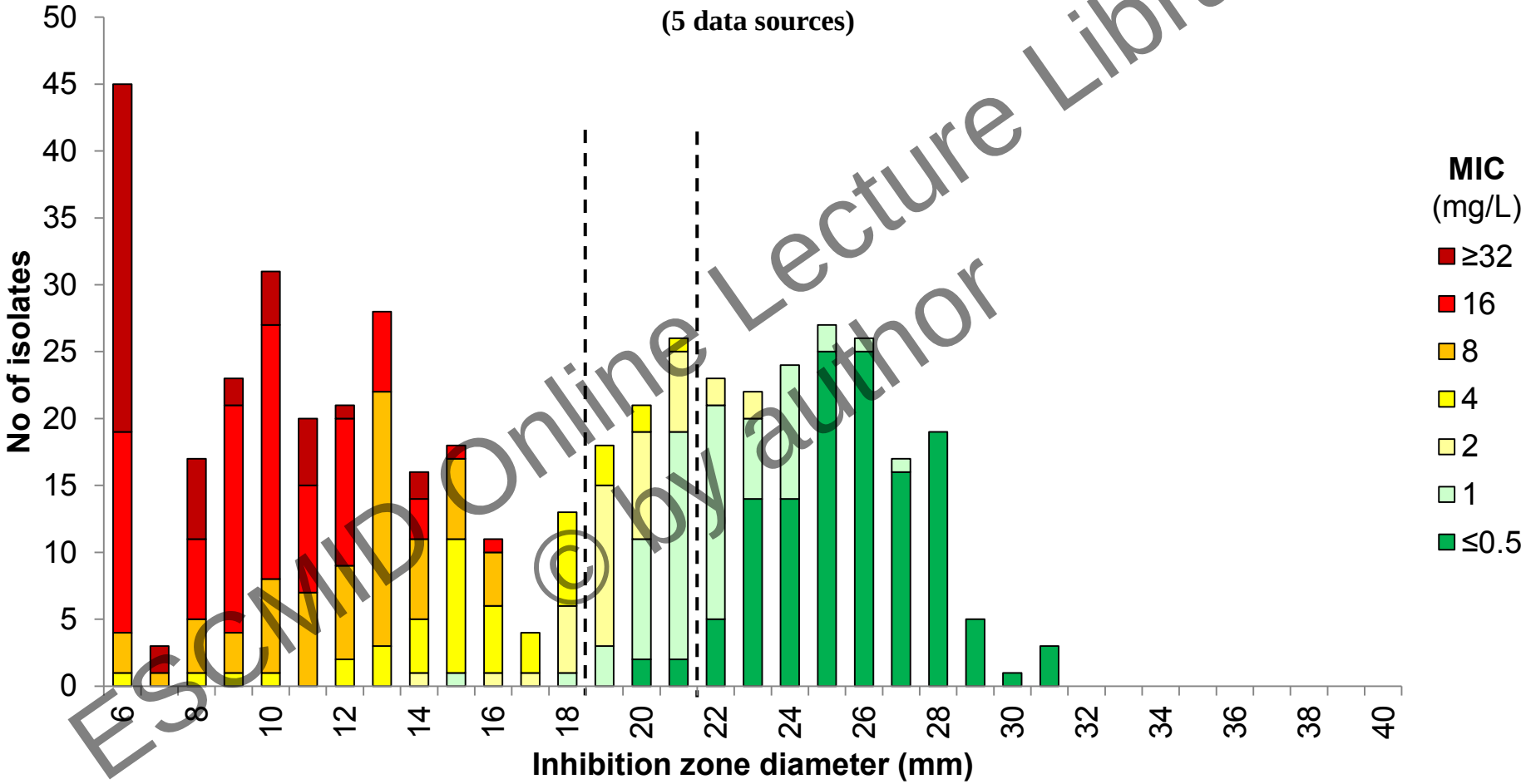
E. coli



JMI Laboratories (courtesy of Prof R. Jones)

Ceftazidime 10 µg vs. MIC
E. coli, 482 clinical isolates

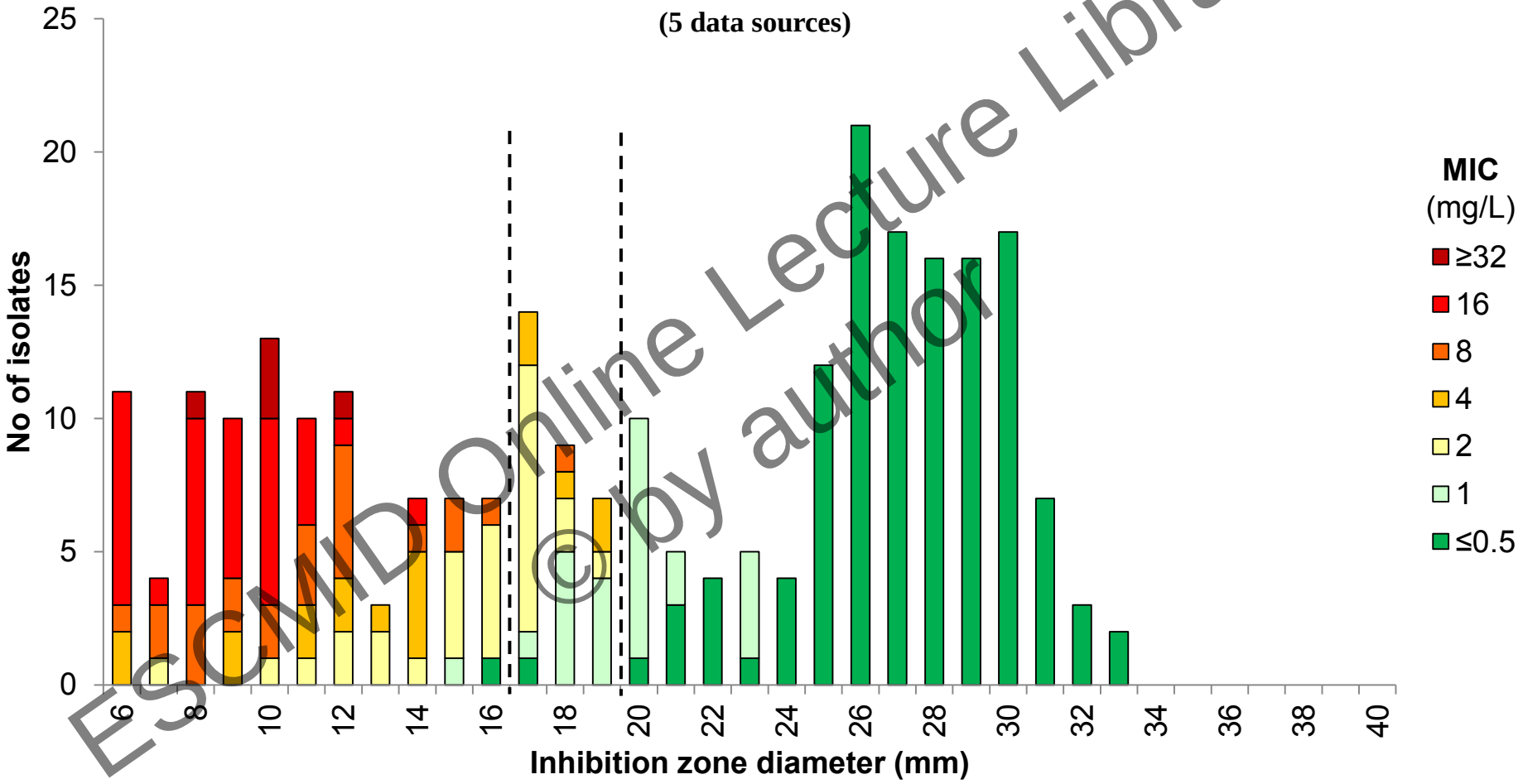
(5 data sources)



Breakpoints		**ECOFF**
MIC	S≤1, R>4 mg/L	0.5 mg/L
Zone diameter	S≥22, R<19 mm	

Courtesy of EDL

Cefotaxime 5 µg vs. MIC
E. coli, 263 clinical isolates



Breakpoints		**ECOFF**
MIC	S≤1, R>2 mg/L	0.25 mg/L
Zone diameter	S≥20, R<17 mm	

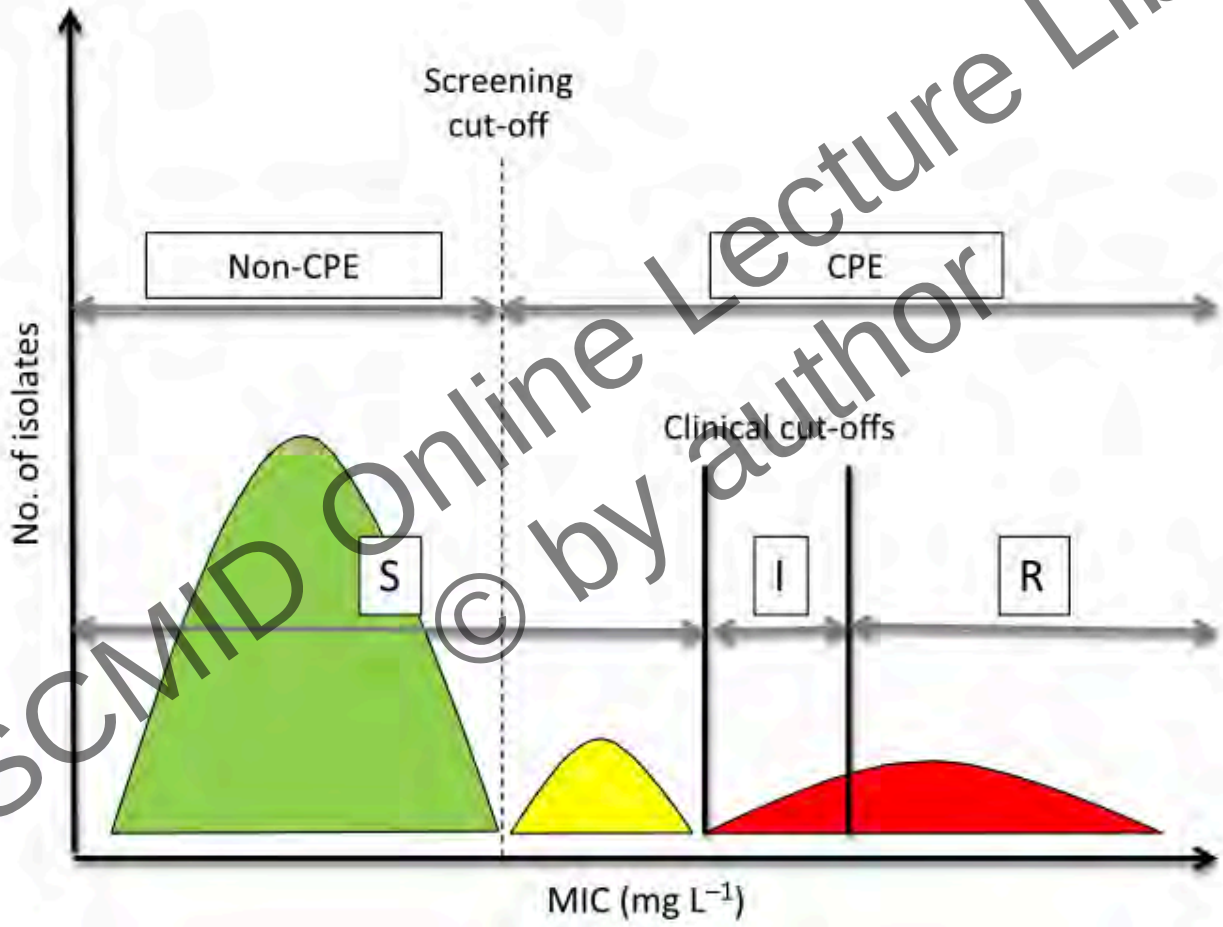
Courtesy of EDL

Preliminary conclusions

- MIC-testing has an inherent biological variation of ± 1 dilution step if done correctly with broth microdilution
  → Potentially less if we included in-between values
- Nowadays not very challenging to carry out BMD on commercial panels (with or without digital reading)
  → But: not allowed to express yourself!
- The EUCAST disk diffusion method has been well calibrated vs BMD, and is an excellent proxy (more conservative estimates)
- If you use other MIC-methods than the reference you are basically on your own, and need to validate the approach yourself

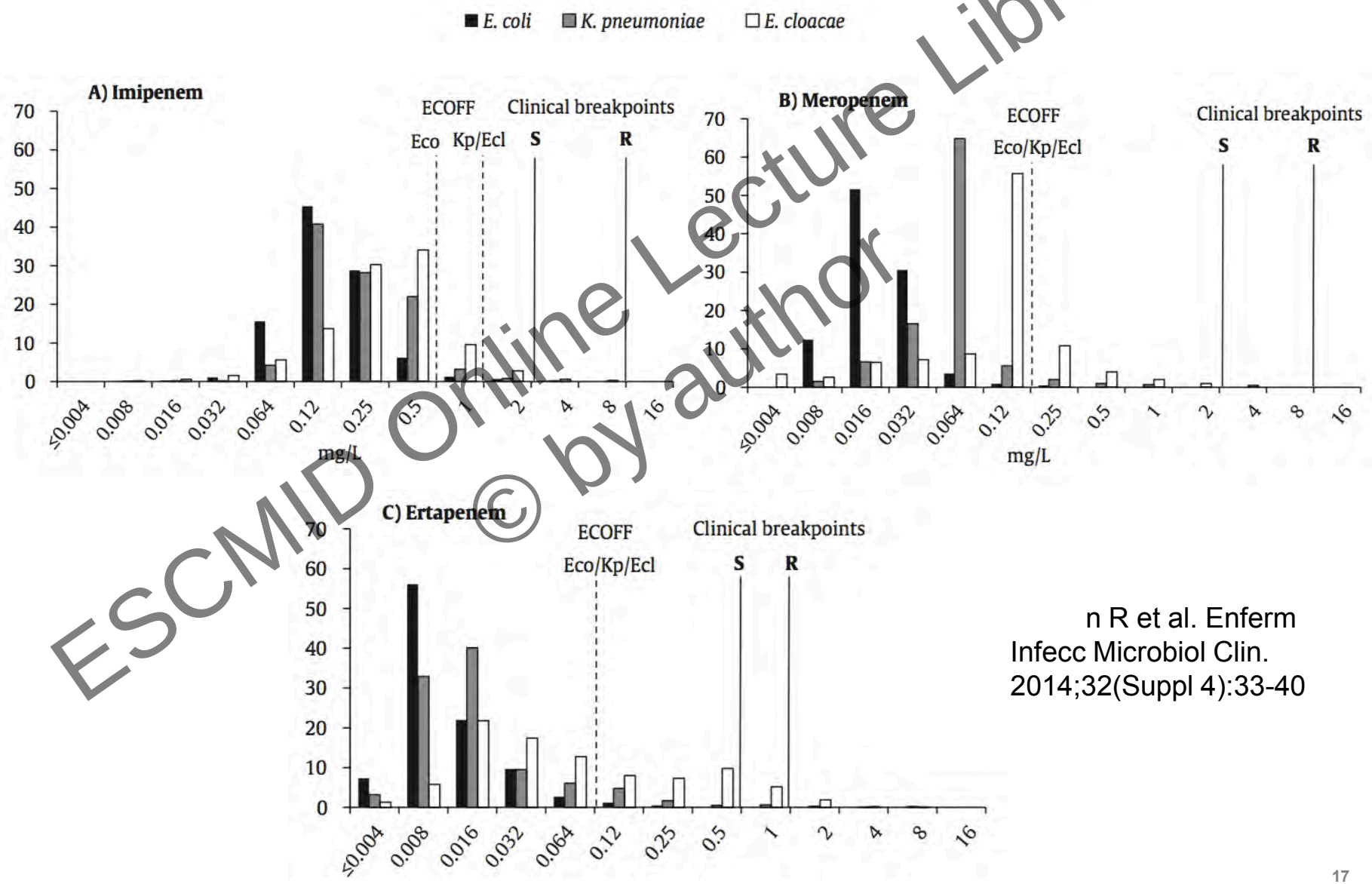
Carbapenems

The complexity of CPE detection



Tängdén T and Giske CG. J Intern Med. 2015;277(5):501-12.

MIC-distributions carbapenems

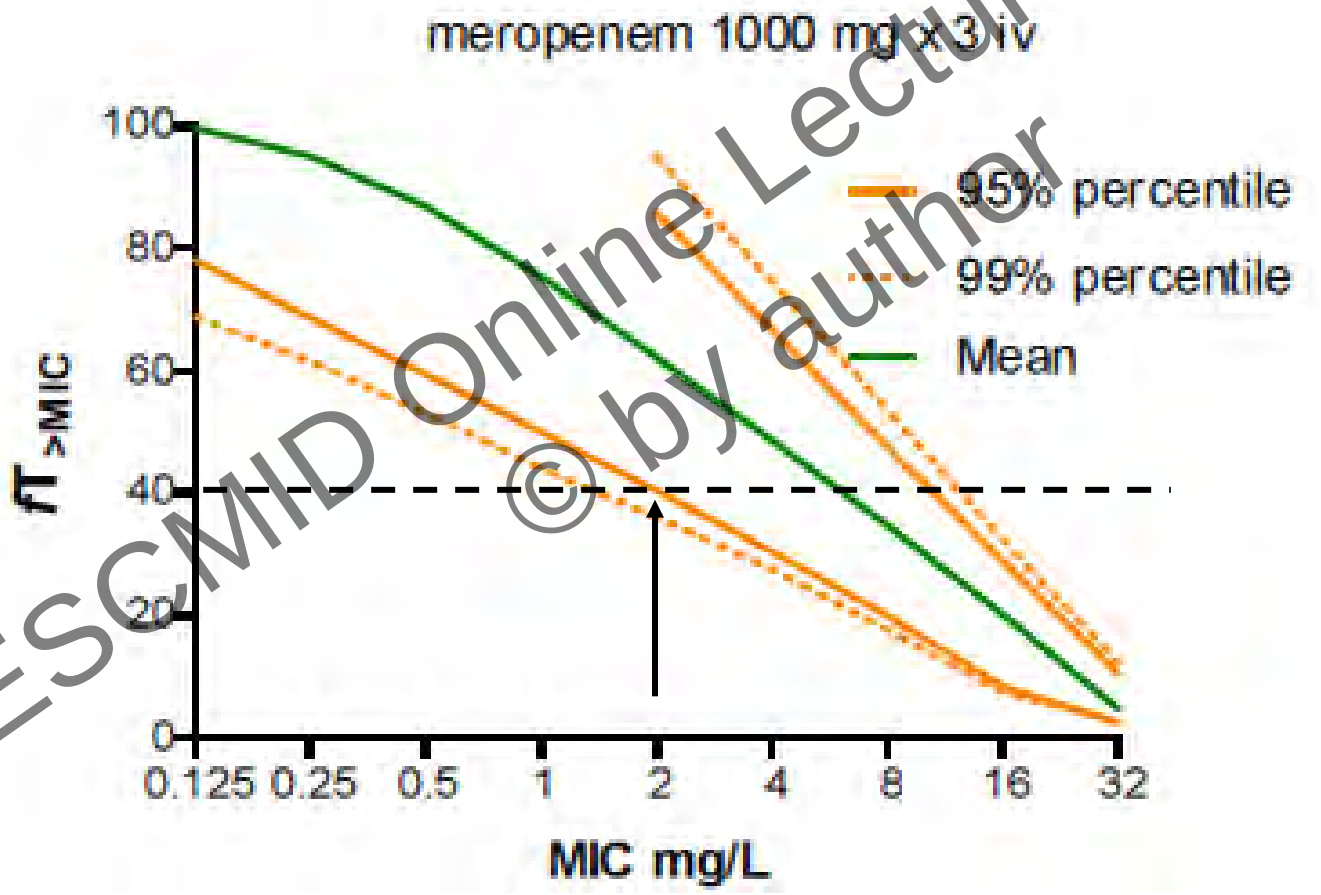


n R et al. Enferm Infecc Microbiol Clin. 2014;32(Suppl 4):33-40

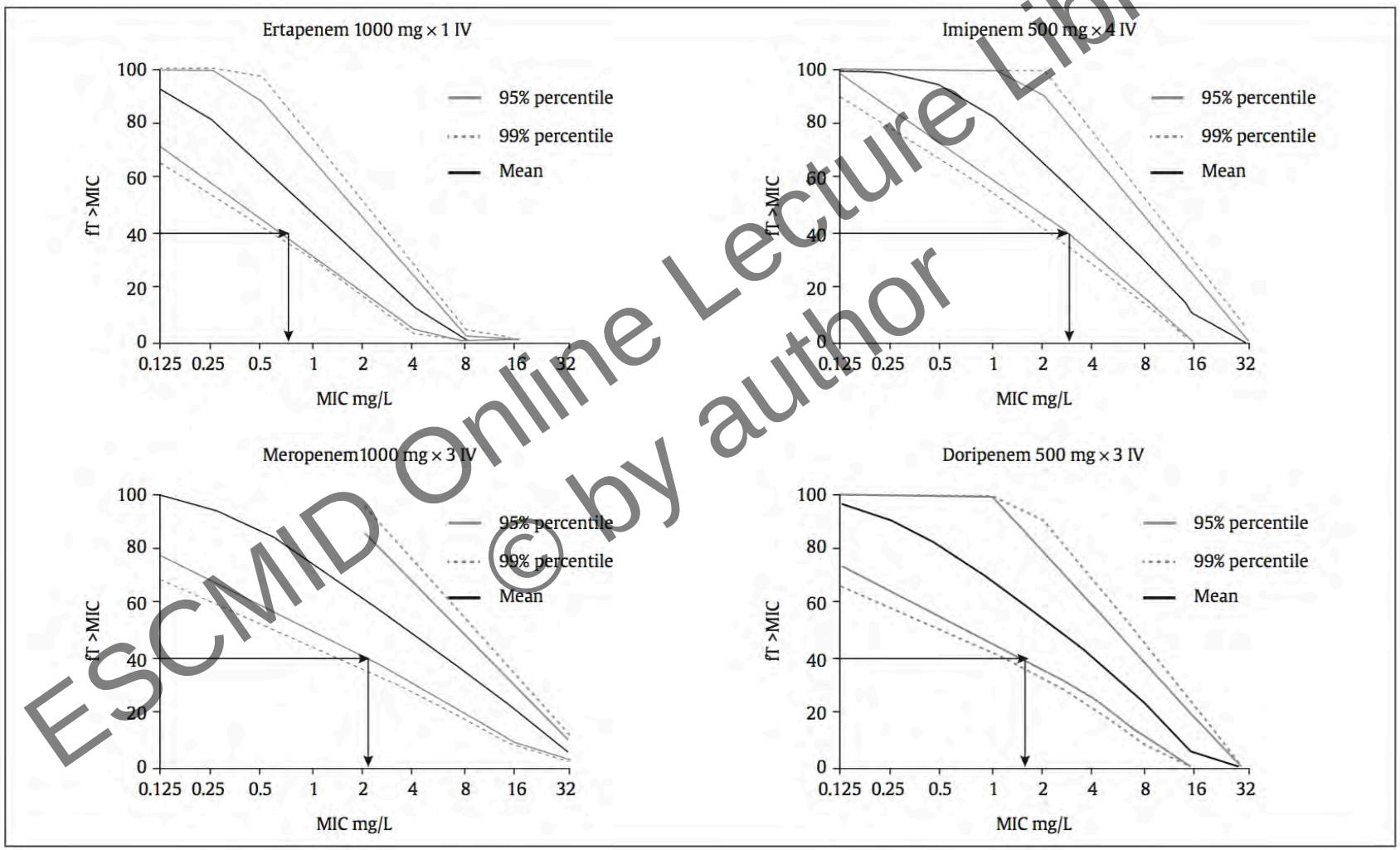
Current carbapenem breakpoints

	FDA	CLSI		EUCAST (EMA)		
	S	S	R	S	R	ECOFF
Imipenem	≤4	≤1 (4)	≥4 (16)	≤2	>8	≤0.5; ≤1
Meropenem	≤4	≤1 (4)	≥4 (16)	≤2	>8	≤0.125
Ertapenem	≤2	≤0.25 (2)	≥1 (8)	≤0.5	>1	≤0.06
Doripenem	≤0.5	≤1 (ND)	≥4 (ND)	≤1	>4	≤0.12

PK/PD for meropenem (EUCAST RD)

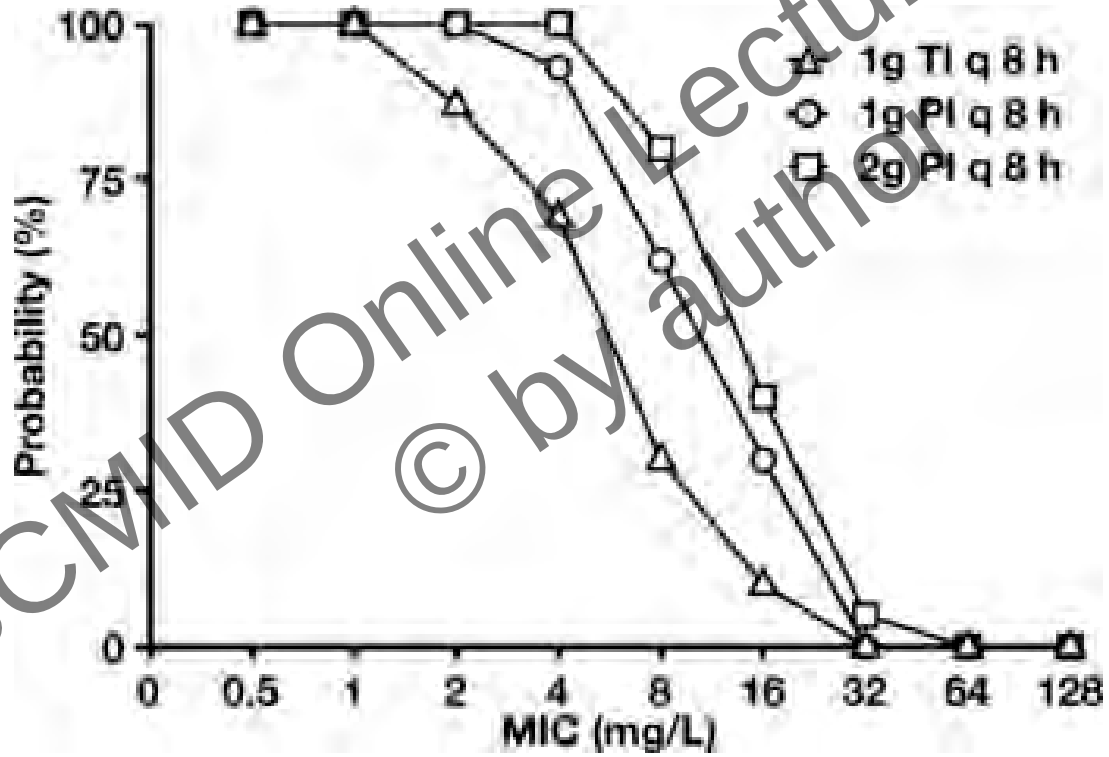


Pharmacodynamic breakpoints



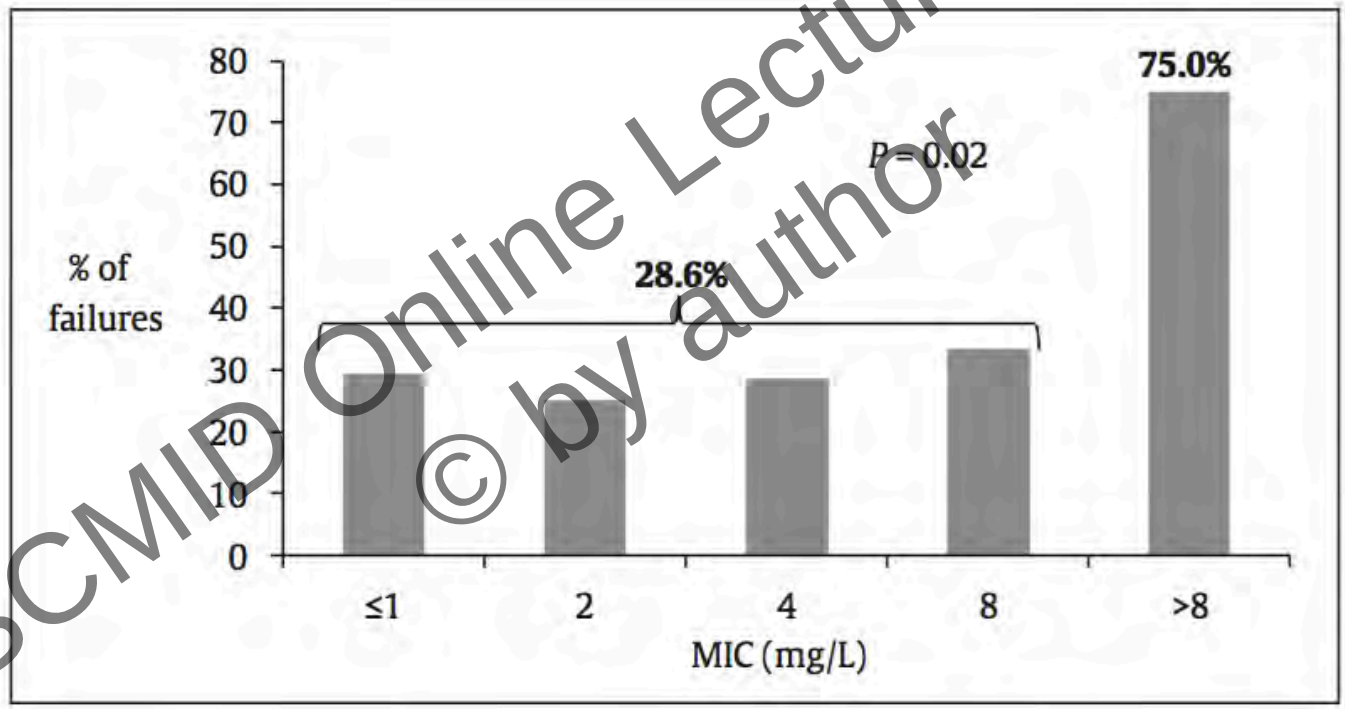
n R et al. Enferm Infecc Microbiol Clin. 2014;32(Suppl 4):33-40

Prolonged infusion or 2 g dosing



Kuti JL et al. J Clin Pharmacol 2003; 43(10):1116-23

Clinical outcomes of carbapenem monotherapy



Tzouvelekis LS et al. Clin Microbiol Rev. 2012;25:682-707.

n R et al. Enferm Infecc Microbiol Clin. 2014;32(Suppl 4):33-40

Bloodstream infections with gram-negative bacilli: CART-analysis

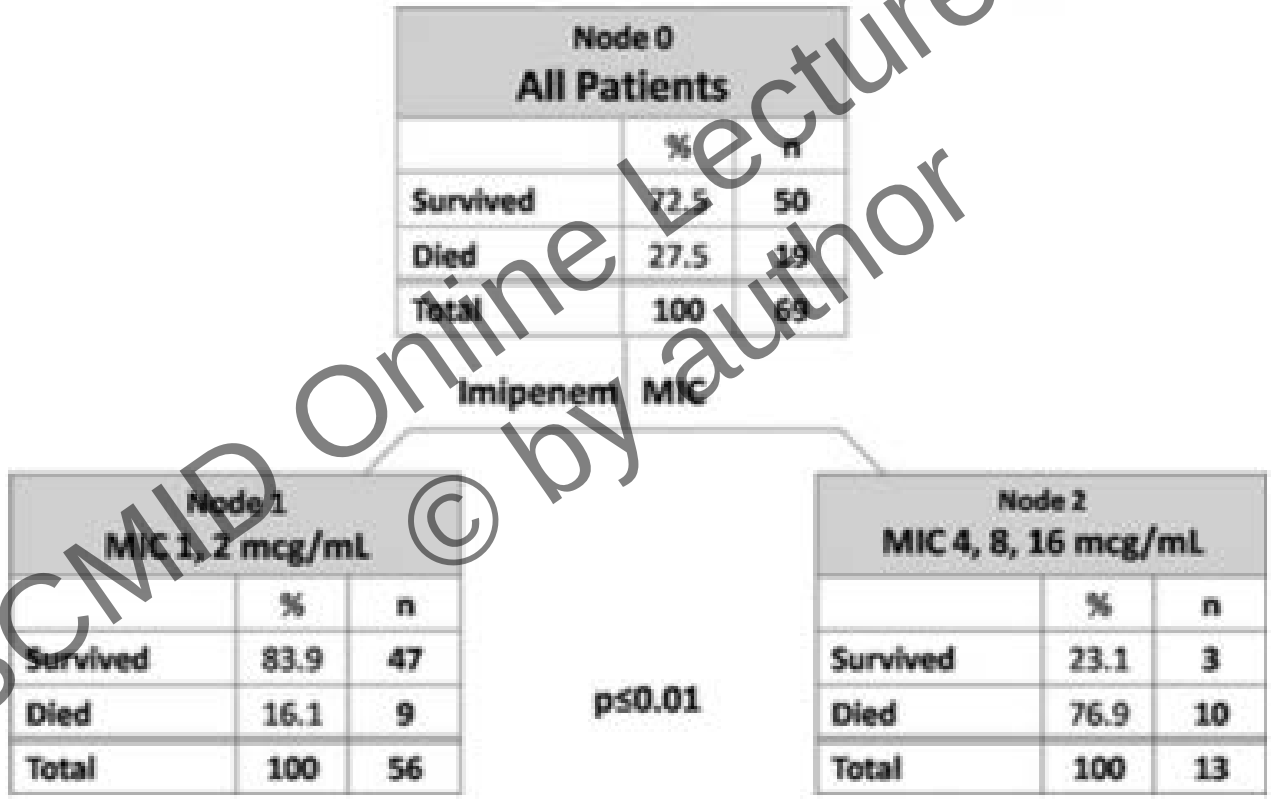
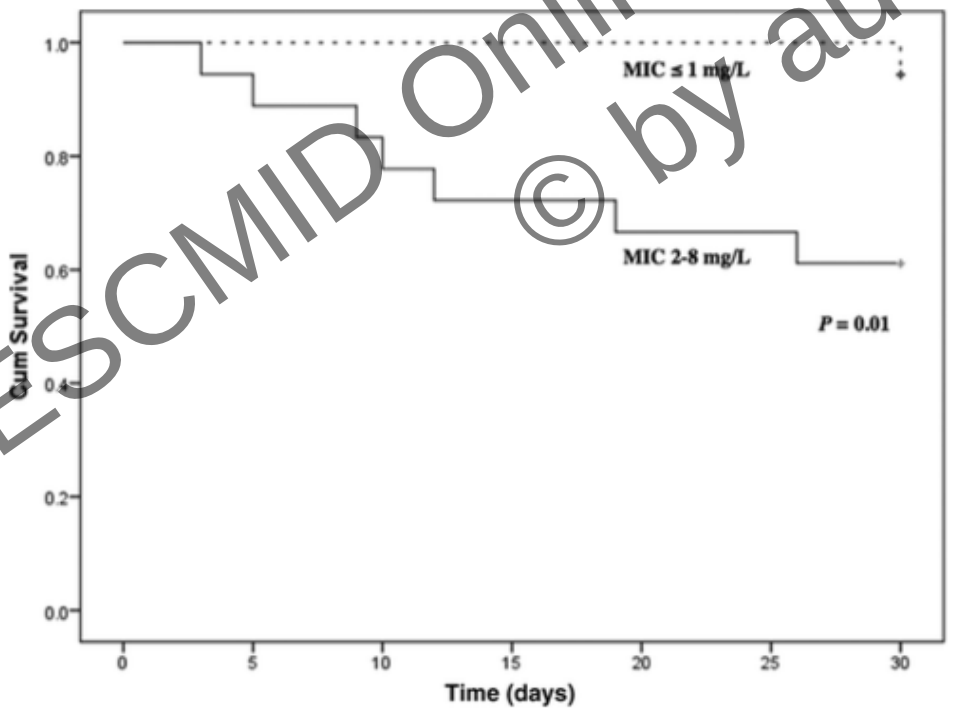


FIG 1 Classification and regression tree model stratifying mortality by MIC.

Esterly JS et al. AAC 2012; 56:4885

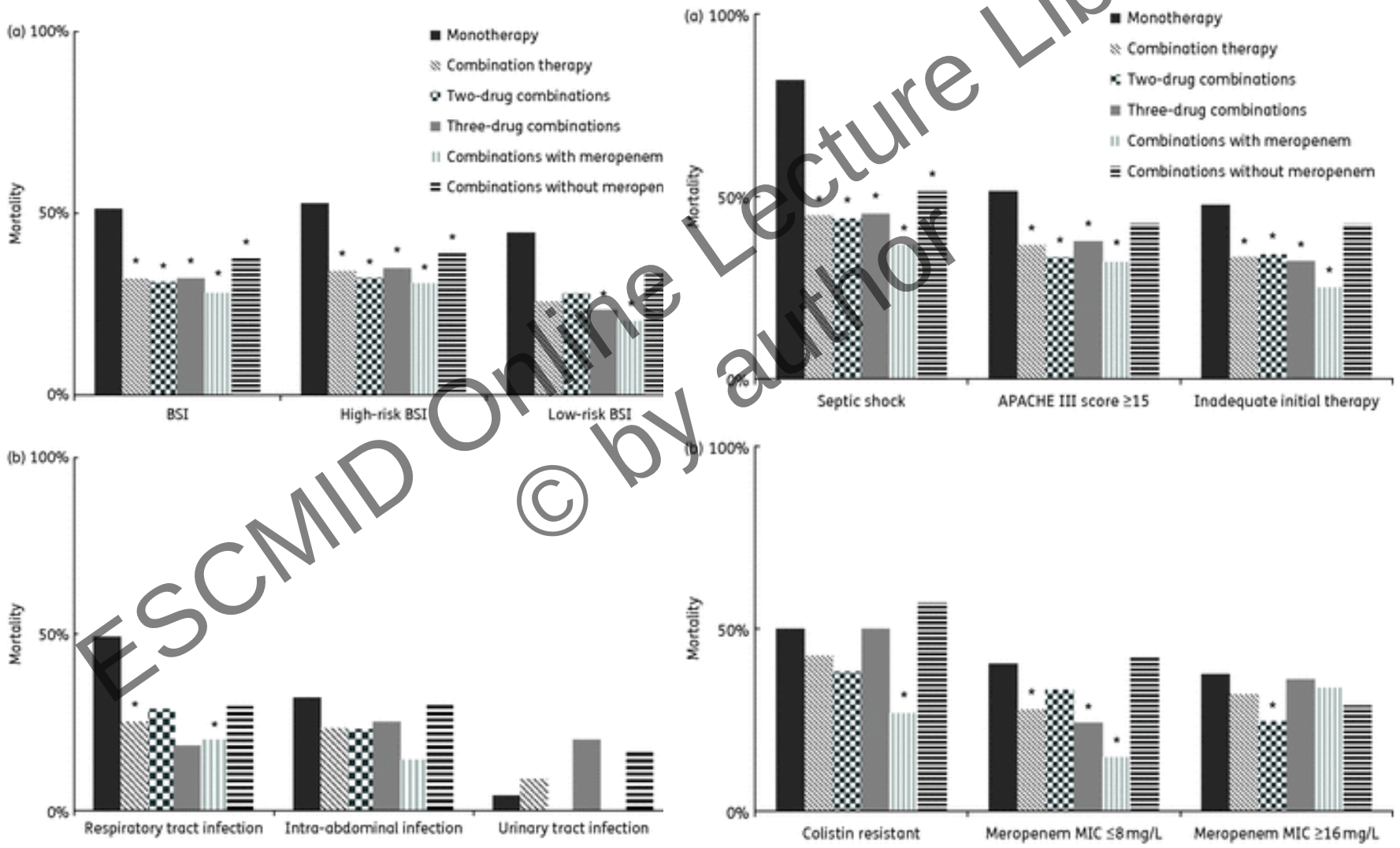
Retrospective matched cohort study, outcomes stratified on carbapenem MICs

Outcome	MIC ≤ 1 mg/L	MIC 2-8 mg/L	P-value
30-d mortality (%)	1/18 (5.6)	7/18 (38.9)	0.04
Length of stay (d)	34.4±25	57.6±45	0.06
ICU stay (d)	21.7±19	56.6±44	<0.01
30-d readmission	3/17 (17.6)	3/11 (27.3)	0.65



Patel TS, Nagel JL.
JCM 2015;53:201

For KPC: combination therapy is superior to monotherapy (n=661)



Tumbarello M et al. JAC 2015; 70(7):2133-43

Comparison of the monotherapy and the combination therapy group

Characteristic	Monotherapy (n=307)	Combination therapy (n=354)	P-value
Age	71	64	<0.001
Hematological malignancy	8.1%	18.1%	<0.001
Neutropenia	5.9%	14.7%	<0.001
BSI	50.8%	82.2%	<0.001
High risk BSI	41.4%	61.3%	<0.001

Tumbarello M et al. JAC 2015; 70(7):2133-43

Combination therapy superior in multivariate analysis

Variable	*P* value	OR (95% CI)
Combination therapy	0.001	0.52 (0.35–0.77)
BSI	<0.001	2.09 (1.34–3.29)
Septic shock at infection onset	0.001	2.45 (1.47–4.08)
APACHE III score	<0.001	1.05 (1.04–1.07)
Chronic renal failure	<0.001	2.27 (1.44–3.58)
Colistin-resistant isolate	0.001	2.18 (1.37–3.46)
Inadequate empirical antimicrobial therapy	0.04	1.48 (1.01–2.18)

- But: we still do not know whether benefit of combination therapy remains for susceptible strains with CPE
- So perhaps combination therapy is always adequate for CRE, but not necessarily all CPE

Critical voices

Journal of Antimicrobial Chemotherapy Advance Access published March 29, 2012

J Antimicrob Chemother
doi:10.1093/jac/dks088

Journal of Antimicrobial Chemotherapy

Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly?

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- Failures occur with carbapenemase-producers
- MICs are not reproducible
- People will stop testing for carbapenemases (and for regular ESBLs) – infection control will not be a strong enough argument

Personal comments regarding these concerns

- The data that exist (and have been reviewed here) are scarce, but if anything supports reporting as found
  → Zero failures can never be expected
- MIC-testing is not an easy task
  → Different methods should be systematically compared with ”difficult” organisms
  → Importantly, the EUCAST disk diffusion method has been calibrated vs MIC-testing and represents an excellent proxy
- **EUCAST has not discouraged laboratories from carbapenemase (or ESBL) testing**

Conclusions

- Broth microdilution MIC data is optimal for management of BSI
- Disk diffusion is an excellent proxy for MIC, but will produce some major errors (to avoid very major errors)
- Detection of resistance mechanisms
  → For infection control: need to have
  → For patient management: nice to have
- Resistance mechanisms frequently lead to clinical failures, but their significance will be determined mainly by resulting MIC